Withania

Withania somnifera (L.) Dunal

Family: Solanaceae (nightshade family). This family is comprised of 84 genera that include about 3000 species. Members of this family are generally annual shrubs.1 The genus Withania is closely related to the genus Physalis, the gooseberries. Physalis somnifera L., Withania kansuensis Kuang & A. M. Lu and Withania microphysalis Suess. are synonyms.[2]

Parts Used: Root

Description: Withania is a small, woody perennial shrub that grows up to one metre in height. It can be found growing in Africa, the Mediterranean and India. As a result of this wide growing range there are considerable morphological and chemotypical variations in terms of local species. However, the primary alkaloids of both the wild and the cultivated species appear to be the same. It has densely velvety stems and leaves, small white or yellowish flowers in short clusters and spherical orange-red berries of about 8mm in diameter. These are completely enclosed in brown papery and bladdery structures formed by the remains of the sepals that enlarge markedly as the fruit develops.[3,4]

Traditional and Empirical Use: Withania, commonly known as ashwagandha, Indian ginseng or winter cherry (not to be confused with Physalis alkekengi, also known as winter cherry), is a revered medicinal plant that has been used in Ayurvedic and indigenous medicine for millennia. Ayurveda, the traditional system of medicine practiced in India, can be traced back to 6000 BC. The genus Withania is named after Henry Witham, an English palaeobotanist of the early 19th century.[5]

The species name somnifera means sleep-inducing in Latin which probably refers to its extensive use as a remedy against stress from a variety of daily chores. The name ashwagandha is a combination of the Sanskrit word ashva, meaning horse and gandha meaning smell. The root has been described as having a strong horse- like aroma, although some experts suggest that the origin of the name implies that one who consumes it can attain the power of a horse. Although it is considered less stimulating, some herbalists refer to withania as Indian ginseng since it is used in India in a similar way to how Eleutherococcus senticosus (Siberian Ginseng) and Panax ginseng (Chinese / Korean Ginseng) are used in traditional Chinese medicine to treat a large variety of human diseases. The fleshy roots are indeed superficially similar to ginseng roots. Various parts of withania (berries, leaves and roots) have been used by Ayurvedic practitioners as folk remedies. The berries are sometimes used as a substitute to coagulate milk in cheese making. It is commonly used in emaciation of children (often given with milk), debility from old age, rheumatism, weakened conditions of vata dosha (an Ayurveydic body/personality type), leucoderma (or vitiligo, a chronic skin disorder that causes de-pigmentation of skin), constipation, insomnia, nervous breakdown and goitre. The paste, formed when roots are crushed with water, is applied to reduce joint inflammation. It is also locally applied in carbuncles, ulcers and painful swellings. The root, in combination with other drugs, is prescribed for scorpion-sting as well as snake venom. Withania glycoprotein inhibits the hyaluronidase activity of cobra (Naja naja) and viper (Daboia russelii) venoms providing some support for this use.[6]

It also helps in leucorrhoea (vaginal discharge), boils, pimples, flatulent colic, worms and piles. The leaves are bitter and are recommended in fever and painful swellings. The flowers are astringent, depurative, diuretic and aphrodisiac. The seeds are anthelmintic. In Ayurveda withania is referred to as a 'rasayana', a group of plant- derived drugs reputed to promote physical and mental

health, augment resistance of the body against disease and diverse adverse environmental factors, revitalise the body in debilitated conditions and increase longevity. These types of remedies are given to small children as tonics and are also taken by the middle-aged and elderly to increase longevity. Among the ayurvedic rasayana herbs, withania holds the most prominent place. It is known as 'Sattvic Kapha Rasayana' herb. Most of the rasayana herbs are adaptogen and anti-stress agents. Withania is commonly available as a churna, a fine sieved powder that can be mixed with water, ghee (clarified butter) or honey. It enhances the function of the brain and nervous system and improves the memory. It improves the function of the reproductive system promoting a healthy sexual and reproductive balance. Being a powerful adaptogen, it enhances the body's resilience to stress. Withania improves the body's defence against disease by improving the cell-mediated immunity. It also possesses potent antioxidant properties that help protect against cellular damage caused by free radicals. In view of its varied therapeutic potential, it has also been the subject of considerable modern scientific attention. Withania roots are a constituent in more than 200 formulations in Ayurveda, Siddha and Unani medicine, which are used in the treatment of various physiological disorders.[7,8,9,10]

Constituents: The chemistry of withania has been extensively studied and more than 80 chemical constituents have been identified, extracted and isolated. The biologically active chemical constituents are alkaloids (isopelletierine, anaferine), steroidal lactones (withanolides, withaferins), saponins containing an additional acyl group (sitoindoside VII and VIII) and withanolides with a glucose at carbon 27 (sitoindoside IX and X). It is also rich in iron, phytosterols (beta-sitosterol, stigmasterol, beta-sitosterol glucoside, stigmasterol glucoside), triterpene (beta-amyrin), Viscosa lactone B, alpha+beta glucose. Much of withania's pharmacological activity has been attributed to two main withanolides, withaferin A and withanolide D.[11,12,13]

Actions: Adaptogen, antistress, mild sedative, nervine tonic, tonic, hypnotic, anti-inflammatory, anti-tumour, antioxidant, immunomodulatory, haemopoietic (the formation of blood).

Pharmacological Activity: Findings from studies on withania clearly indicate that its traditional use has a logical and scientific basis however large scale clinical studies are needed to prove the clinical efficacy of this herb, especially in stress related diseases, neuronal disorders and cancers.14 Withania and several of its key constituents have been subjected to scientific investigations in vitro and in vivo. Whilst the pharmacological actions of individual components is important to understand, clinical effects are difficult to predict from these studies as the ultimate effect of the herbal treatment will be the result of many intraherbal interactions.15 This monograph will focus on whole herb studies.

Adaptogenic and anti-stress activity: The findings of a 2012 single centre, prospective, double-blind, randomised, placebo-controlled trial suggest that a high-concentration full-spectrum withania root extract safely and effectively improves an individual's resistance towards stress and thereby improves self-assessed quality of life. A total of 64 subjects with a history of chronic stress were enrolled into the study after performing relevant clinical examinations and laboratory tests. These included a measurement of serum cortisol, and assessing their scores on standard stress-assessment questionnaires. They were randomised to either the placebo control group or the study drug treatment group, and were asked to take one capsule twice a day for a period of 60 days. In the study drug treatment group, each capsule contained 300 mg of high-concentration full-spectrum extract from the root of withania. During the treatment period (on day 15, day 30 and day 45), a follow-up telephone call was made to all subjects to check for treatment compliance and to note

any adverse reactions. Final safety and efficacy assessments were done on day 60. The treatment group that was given the withania exhibited a significant reduction ($p < 0.0001$) in scores on all the stress-assessment scales on day 60, relative to the placebo group. The serum cortisol levels were substantially reduced ($p = 0.0006$) in the withania group, relative to the placebo group.[16]

A six-week, double-blind, randomised controlled trial was conducted to evaluate the efficacy of an ethanolic extract of withania (500mg twice daily) in 39 patients with a range of ICD-10 (International Statistical Classification of Diseases and Related Health Problems, tenth revision) anxiety disorders. Twenty patients received the drug and 19 received placebo. At two and six weeks follow-up, data from approximately 85% of patients in each group was available for analysis. Statistical trends favouring withania were observed at both time points.[17]

There have been extensive studies using animal models demonstrating the adaptogenic and anti-stress properties of withania. Studies have shown it to be effective in increasing stamina (physical endurance) and preventing stress induced gastric ulcer, carbon tetrachloride (CCl_4) induced hepatotoxicity and mortality. Its antistressor properties were investigated in a study using rats and cold water swimming stress test. The results indicated that the withania treated animals show better stress tolerance.[18]

There are reports showing that withania possesses antioxidant, adaptogenic and aphrodisiac activities apart from having some neurotransmitters. A recent human trial confirms these properties, along with demonstrating its capability to improve male factor fertility in idiopathic (unknown cause) cases. Stress has been reported to be a causative factor for male infertility. A human trial was conducted to understand the role of stress in male infertility, and to test the ability of withania to combat stress and treat male infertility (see also spermatogenic activity below). A total of 121 men were selected for the study.

Normozoospermic (normal semen) but infertile individuals were chosen and further categorised into three groups: normozoospermic heavy smokers, normozoospermics under psychological stress and normozoospermics with infertility of unknown etiology. Normozoospermic fertile men were recruited as controls. The infertile men were prescribed withania root powder, orally, in a single dose (5 g/day) for three months with a cup of skimmed milk. Measuring various biochemical and stress parameters before and after treatment, suggested a definite role of stress in male infertility and the ability of withania to treat stress-related infertility. Treatment resulted in a decrease in stress, improved the level of antioxidants and improved overall semen quality in a significant number of individuals. The treatment resulted in pregnancy in the partners of 14% of the patients. The authors found that among withania's major effects, it balances hormone levels, reduces oxidative stress and possibly improves detoxification processes in the body. In an earlier study, it was shown that disturbed hormone levels correlate well with infertility; therefore, correction of this imbalance by withania could be one of the major factors contributing to fertility improvement. Interestingly, the authors stated that it could be a combination of direct and indirect effects of this herb to combat stress by pleuripotent (the ability of certain substances to produce several distinct biological responses) effecter constituents. They said "It would be worthwhile to stress that such an effect is more likely in its natural mixture form than isolating one or more individual fractions that may not yield similar effects. However, it is still a good idea to fractionate this herb to understand its mechanism of action."[19]

The results of an Indian in vivo study indicate that withania has significant anti-stress and adaptogenic activity, confirming the clinical use of the plant in Ayurveda.

The adaptogenic activity of a standardised extract of withania roots was investigated against a rat model of chronic stress (CS). The stress procedure was mild, unpredictable footshock, administered once daily for 21 days to adult male Wistar rats. CS induced significant hyperglycaemia, glucose intolerance, increase in plasma corticosterone levels, gastric ulcerations, male sexual dysfunction, cognitive deficits, immunosuppression and mental depression. These CS induced perturbations were attenuated by withania (25 and 50 mg/kg orally), administered one hour before footshock for 21 days.[20]

A withanolide-free hydrosoluble fraction was isolated from the roots of withania. It exhibited significant anti-stress activity in a dose-related manner and was further studied against chemical and physical induced stress in rats and mice.[21]

A methanolic extract of withania root was found to inhibit the specific binding of gamma-aminobutyric acid (GABA) ligands and enhanced the binding of flunitrazepam (also known as Rohypnol, an intermediate acting benzodiazepine used as a hypnotic, sedative, anticonvulsant, anxiolytic and skeletal muscle relaxant drug) to their receptor sites, displaying GABA-mimetic activity.[22]

Sedative activity: The alkaloids in withania are said to be sedative and reduce blood pressure and heart rate.23 An Indian study explored the role of withania root extract in sleep-disturbed rats. The results suggest the involvement of a GABA-ergic mechanism in the sleep promoting effects of withania in a sleep-disturbed state.24 An earlier study by the same authors investigated the protective effect of withania on the behavioural and biochemical alterations in sleep disturbed mice. The results suggested that withania root extract can be used in the management of sleep loss and associated oxidative stress. Pretreatment with withania root extract (100 and 200 mg/kg) and diazepam (0.5 mg/kg) significantly protected reduction in body weight, improved the reduced locomotor activity and anxiety levels in animals.[25]

Nervous system activity: Cognitive enhancement. The results of a 2014 prospective, double-blind, multi- dose, placebo-controlled, crossover study suggest that withania extract can improve cognitive and psychomotor performance and may, therefore, be a valuable adjunct in the treatment of diseases associated with cognitive impairment. The Indian study involved an assessment of cognitive and psychomotor effects of withania extract in healthy human participants. Twenty healthy male participants were randomised to receive 250 mg two capsules twice daily of an encapsulated dried aqueous extract of roots and leaves of withania or a matching placebo for a period of 14 days. Cognitive and psychomotor performance was assessed pre-dose (day 1) and at three hours post-dose on day 15 using a battery of computerised psychometric tests. After a washout period of 14 days, the subjects crossed-over to receive the other treatment for a further period of 14 days as per prior randomisation schedule. The same battery of test procedures was performed to assess cognitive and psychomotor performance. Significant improvements were observed in reaction times with simple reaction, choice discrimination, digit symbol substitution, digit vigilance and card sorting tests with withania compared to placebo.[26]

The cognitive effects of a standardised extract of the withania (oral Sensoril) showed promise in bipolar disorder in an eight week, double-blind, placebo-controlled, randomised 2013 study. Sixty euthymic (normal mood) subjects with DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision) bipolar disorder were enrolled in the study of withania (500 mg/d) as a procognitive agent added adjunctively to the medications being used as maintenance treatment for bipolar disorder.

Although results are preliminary, withania appears to improve auditory-verbal working memory (digit span backward), a measure of reaction time, and a measure of social cognition in bipolar disorder. The authors concluded that given the small amount of data for improving cognitive capacity in bipolar disorder, withania offers promise, appears to have a benign side-effects profile, and merits further study.[27]

The results of an in vitro study may partially substantiate the traditional use of withania for improvement of cognition. The Indian study showed that a methanolic extract of withania had potent acetylcholinesterase inhibitory activity.[28]

Withania exhibited a memory enhancing effect in mice in an Indian study. Daily administration of withania for six days significantly improved memory consolidation in mice receiving chronic electroconvulsive shock treatment.[29]

An earlier German study was conducted to assess whether the memory-enhancing effects of plant extracts from withania are owing to neurochemical alterations of specific transmitter systems. The data suggested withania affects, preferentially, events in the cortical and basal forebrain cholinergic signal transduction cascade. The authors concluded that the drug-induced increase in cortical muscarinic acetylcholine receptor capacity might partly explain the cognition-enhancing and memory-improving effects of extracts from withania observed in animals and humans.[30]

Neuroprotective activity: Parkinson's disease is a neurodegenerative disorder and currently significant emphasis is given to the treatment of this disease using herbal medicines. A 2013 study evaluated the neuroprotective effect of withania extract on Parkinsonian mice. The mice were divided into three groups; the first group served as control, the second group was given maneb (MB) and paraquat (PQ) and the last group was administered MB-PQ along with withania for three, six and nine weeks. Maneb is a foliate fungicide used to create a toxin-based animal model of Parkinson's disease and paraquat is a herbicide linked to Parkinson's disease. The behavioural studies showed a significant improvement in the motor movement patterns and gripping ability of withania exposed Parkinsonian mice. The results clearly indicated the usefulness of withania in providing protection against MB-PQ induced nigrostriatal (one of the major dopamine pathways in the brain involved particularly in the production of movement) dopaminergic neurodegeneration and marked improvement in the behavioural, anatomical and biochemical deformities.[31]

A 2013 animal study found that withania has neuroprotective and prophylactic potential. Withania improved hypobaric hypoxia (HH) induced memory impairment and neurodegeneration in the rat hippocampus through nitric oxide mediated modulation of corticosterone levels. Administration of withania prevented HH induced memory impairment and neurodegeneration along with decreased nitric oxide, corticosterone, oxidative stress and acetylcholinesterase activity in the hippocampal region.[32]

In an earlier study the neuroprotective effects of withania were studied on stressed rats. Treatment with withania significantly reduced (80%) the number of degenerating cells in both the areas. The study thus demonstrates the anti-stress and neuroprotective effects of withania.[33]

Another indication for withania's potential to protect neurons was demonstrated in a study which found the methanol extract of withania promotes the formation of dendrites. Extension of dendrites and axons in neurons may compensate for and repair damaged neuronal circuits in the dementia brain.[34]

The findings of an Indian study suggest that phytochemicals present in withania mitigate the effects of excitotoxicity (pathological process by which nerve cells are damaged and killed by excessive stimulation by neurotransmitters) and oxidative damage in the hippocampus and this might be accomplished by their antioxidative properties.[35]

Anti-inflammatory activity: A 2014 study has found that withania acts as an anti- inflammatory and antioxidant agent in decreasing the arthritic effects in collagen-induced arthritic rats and has a protective effect against collagen-induced arthritis in rats. The study focused on the effect of withania root powder on the behavioural and radiological changes in collagen-induced arthritic rats. Administration of withania root powder (600 mg kg(-1)) to the arthritic rats significantly decreased the severity of arthritis by effectively suppressing the symptoms of arthritis and improving the functional recovery of motor activity and radiological score.[36]

A recent in vitro study has shown direct, statistically significant, anti-inflammatory effects of an aqueous extract of withania on human osteoarthritis cartilage. Withania significantly decreased nitric oxide release in one subset of patients.[37]

The transcription factor nuclear factor-kappaB (NF-kappaB) plays a critical role in normal and pathophysiological immune responses. Therefore, NF-kappaB and the signalling pathways that regulate its activation have become a major focus of drug development programs. The results of a 2007 Belgian study indicate that withanolides can be considered as a novel class of NF-kappaB inhibitors, which hold promise as novel anti-inflammatory agents for treatment of various inflammatory disorders and/or cancer.[38]

Several genes that regulate cellular proliferation, carcinogenesis, metastasis and inflammation are regulated by activation of NF-kappaB. A recent in vitro study investigated the effect of withanolides on NF-kappaB and NF-kappaB-regulated gene expression activated by various carcinogens. Overall, the results indicated that withanolides inhibit activation of NF-kappaB and NF-kappaB-regulated gene expression, which may explain the ability of withanolides to enhance apoptosis and inhibit invasion and osteoclastogenesis.[39]

Anti-osteoporotic activity: Withania treatment markedly prevented changes in ovariectomised (OVX) rats and thus may be a potential agent in the treatment of osteoporosis. A recent Indian study examined the effect of an ethanolic withania extract, which contained oestrogen-like withanolides, for anti- osteoporotic activity.[40]

Anti-tumour activity: A 2013 American study has found withania may enhance anti-tumour function of natural killer (NK; a type of white blood cell) cells. This study may be useful for a clinical study to determine the effects of dietary withania on NK cell immune function in patients with ovarian cancer. Ovarian cancer (OVCA) disseminates in a distinct pattern through peritoneal metastasis and little is known about the immunosuppression in the tumour microenvironment. The goal of the study was to determine changes in NK cell population during OVCA development and the effects of withania supplementation on NK cell localisation in laying hens with OVCA. The results of this study suggest that the population of stromal and tumour-infiltrating NK cells is increased by dietary withania supplementation.[41]

An Indian study has found that withania may be useful in the management of malignancy by targeting multiple pathways. The results of the study demonstrate that withania exhibited selective cytotoxicty against a panel of human

cancer cell lines in vitro compared to normal cells and effectively inhibited tumour growth in mouse tumour models. Besides its anti-tumour effect, withania also stimulated the cell-mediated Th1 (a type of T helper cell) immune response in tumour-bearing mice.[42]

The Chinese Hamster ovary (CHO) cell line is widely used for measuring drug cytotoxicity and resistance. Withania caused a reproducible, dose dependent, inhibition of colony formation of CHO cells. The authors said this knowledge will assist oncologists who plan to use withania extracts as 'synergisers' with conventional chemotherapy or radiation therapy.[43]

An article reviewing the literature pertaining to withania and its botanical constituents as anti-tumour agents, in conjunction with radiation and chemotherapy treatment, concluded that it reduces tumour cell proliferation while increasing overall animal survival time. A search of MEDLINE and EBSCO databases was conducted. Withania was also shown to enhance the effectiveness of radiation therapy while potentially mitigating undesirable side effects. It also reduces the side effects of chemotherapeutic agents cyclophosphamide and paclitaxel without interfering with the tumour-reducing actions of the drugs. These effects have been demonstrated in vitro on human cancer cell lines, and in vivo on animal subjects, but there have been no human trials to date. Given its broad spectrum of cytotoxic and tumour-sensitising actions, the author concluded that withania presents itself as a novel complementary therapy for integrative oncology care.[44]

The effect of withania on the functions of macrophages obtained from mice treated with the carcinogen ochratoxin A (OTA) was investigated in an Indian study. The chemotactic (movement of an organism in response to a chemical stimulus) activity of murine macrophages significantly decreased after 17 weeks of treatment with OTA compared with controls. Production of interleukin-1 (IL-1) and tumour necrosis factor (TNF) was also markedly reduced. Treatment with withania significantly inhibited OTA-induced suppression of chemotactic activity and production of IL-1 and TNF-alpha by macropahges. It was also found that withania treated macrophage chemotaxis when compared with controls.[45]

A study of the anti-tumour and radiosensitising properties of withania has yielded encouraging results. The alcoholic extract of the dried roots of the plant, as well as the active component withaferin A isolated from the extract, showed significant anti-tumour and radiosensitising effects in experimental tumours in vivo, without any noticeable systemic toxicity. Withaferin A gave a sensitiser enhancement ratio of 1.5 for in vitro cell killing of V79 Chinese hamster cells at a non-toxic concentration of approximately 2 microM. The mechanism of action of this compound is not known. The studies so far indicate that withania could prove to be a good natural source of a potent and relatively safe radiosensitiser/chemotherapeutic agent. Further studies are needed to explore the clinical potential of this plant for cancer therapy.[46]

Chemotherapeutic activity: Withania may play a role in protection against cardiotoxicity and thus might be a useful adjuvant therapy where doxorubicin (trade name Adriamycin; a drug used in cancer chemotherapy and derived by chemical semisynthesis from a bacterial species) is the cancer- treating drug. The therapeutic value of doxorubicin as an effective antineoplastic agent is limited by its cardiotoxic side-effects. The administration of doxorubicin (10 mg/ kg) to male Wistar rats induced necrosis and apoptosis in heart tissues. It also caused oxidative stress damage as evidenced by the elevation of malondialdehyde and protein carbonyl levels and catalase activity, accompanied by the concurrent depletion of total antioxidant capacity and of superoxide dismutase level in cardiac tissues.

Most of these doxorubicin-induced biochemical and histological alterations were effectively attenuated by prior administration of purified standardised extract (1.5% withanolides; manufactured by Idea Sphere Inc., American Fork, UT, USA) of withania (300 mg/kg).[47]

The combination of paclitaxel (a drug used in cancer chemotherapy that inhibits cell division) with withania could effectively treat benzo(a)pyrene-induced lung cancer in mice by offering protection from reactive oxygen species damage and also by suppressing cell proliferation. The data suggests that paclitaxel, administered with withania, may extend its chemotherapeutic effect through modulating protein-bound carbohydrate levels and marker enzymes, as they are indicators of cancer.[48]

Administration of an extract from withania (20 mg/dose/ animal; i.p.) for five days along with cyclophosphamide (CTX) (1.5 mmol/kg body wt. i.p.) reduced the CTX induced urotoxicity in an in vivo study. Morphological analysis of the bladders of the CTX-treated group showed severe inflammation and dark colouration whereas CTX along with the withania-treated group showed normal bladder morphology. The extract was found to reduce the protein level in the serum (7.92 g/l) after four hours of CTX treatment, which was higher in the CTX alone- administered group (11.44 g/l). Blood urea N2 (nitrogen) level which was drastically enhanced (136.78 mg/100 ml) after the CTX treatment was significantly reduced (52.08 mg/100 ml) when the animals were treated with withania extract. Similarly, the glutathione (GSH) content in both bladder (1.55 micromol/mg protein) and liver (3.76 micromol/mg protein) was enhanced significantly ($p < 0.001$) in the withania-treated group compared with the CTX alone-treated animals (bladder 0.5 micromol/mg protein; liver 1.2 micromol/mg protein). Histopathological (microscopic examination) analysis of the bladder of CTX alone-treated group showed severe necrotic damage whereas the withania somnifera-treated group showed normal bladder architecture.[49]

A protective effect in CTX-induced myelosuppression was observed in animals treated with withania, revealing a significant increase in white blood cell counts and platelet counts.[50]

Immune and haemopoietic activity: An in vivo study investigated the immunologic effects of withania on four types of immune cells in a human sample to determine the immunologic mechanism. Five participants consumed 6mL of a withania root extract and whole milk twice daily for 96 hours. At 96 hours of use, mean values of receptor expression for all measured receptor types were increased over baseline, indicating that a major change in immune cell activation occurred across the sample. The authors concluded that the effects on immune cell activation with use of withania warranted further study.[51]

A study investigating chronic stress-induced alterations on Th1 lymphocyte subset distribution and corresponding cytokine secretion patterns in mice has found withania causes a significant increase in the stress- induced depleted T-cell population and increases the expression of Th1 cytokines in chronically stressed mice.[52]

Improved haematopoiesis[53] and significant increases in haemoglobin concentration, red blood cell count, white blood cell count and platelet count have been observed in vivo. The immunomodulatory activity of withania was studied in mice with myelosuppression induced by one or more of the following three compounds: cyclophosphamide, azathioprin or prednisolone. A significant modulation of immune reactivity was observed in all the three animal models used. Withania prevented myelosuppression in mice treated with all three immunosuppressive drugs tested.

A significant increase in haemoglobin concentration, red blood cell count, white blood cell count, platelet count and body weight was observed in withania- treated mice as compared with untreated (control) mice. The authors also reported an immunostimulatory activity: treatment with withania was accompanied by significant increases in haemolytic antibody responses towards human erythrocytes.[54]

Antioxidant activity: Reported antioxidant properties include prevention of lipid peroxidation in rats. A study was carried out to evaluate the antiperoxidative effect of withania on liver lipid peroxidation and antioxidant status in adjuvant induced arthritic rats. Results were compared with those for Indomethacin, a non-steroidal anti-inflammatory drug. The antiperoxidative effect of withania root powder was investigated by measuring changes in lipid peroxidation and the antioxidant status of liver in arthritic animals. The oral administration of withania (1000 mg kg-1 b.wt.) modulated the above altered lipid peroxidation and antioxidant status to near normal levels in arthritic animals.[55]

Spermatogenic activity: Numerous human and animal studies have validated the aphrodisiac and testosterone-enhancing effects of withania. Experimental studies have shown that treatment with withania induced testicular development and spermatogenesis in immature Wistar rats by directly affecting the seminiferous tubules, improved prosexual behaviour of sexually sluggish mice, and increased testicular daily sperm production and serum testosterone level.[56,57,58,59]

It has been well documented that high levels of reactive oxygen species (ROS) in the semen induce oxidative damage to the sperm and are associated with abnormal sperm parameters leading to infertility. Withania has been found to counteract the formation of ROS in infertile men.[60,61,62,63,64]

A 2013 pilot study has suggested the potential role of withania in treating male infertility. The study indicated that treatment with a high-concentration, full-spectrum root extract of withania results in significantly improved semen parameters together with improved, and regulated, sexual hormone levels in oligospermic males. The analyses of the data indicated significantly increased sperm concentration and overall motility, which are regarded as the most important criteria for normal fertilising ability of the spermatozoa. The study outcome showed significant enhancement of the semen volume in the withania-treated infertile males. Forty-six male patients with oligospermia (sperm count < 20million/mL semen) were enrolled and randomised either to treatment (n = 21) with a full-spectrum root extract of withania (675mg/d in three doses for 90 days) or to placebo (n = 25) in the same protocol. Semen parameters and serum hormone levels were estimated at the end of 90-day treatment. There was a 167% increase in sperm count, 53% increase in semen volume and 57% increase in sperm motility on day 90 from baseline. The improvement in these parameters was minimal in the placebo-treated group. Furthermore, a significantly greater improvement and regulation was observed in serum hormone levels with the withania treatment as compared to the placebo. In the study, treatment with the withania root extract resulted in a higher level of testosterone and a concomitant increase in serum levels of luteinizing hormone among infertile men having suboptimal testosterone levels before therapy. Apart from spermatogenesis, testosterone also controls the functional competence of the accessory sex organs, as adequate seminal fluid is necessary for the survival and motility of spermatozoa. Thus, it was postulated that the probable reasons for the increased sperm concentration and motility in the findings lie in the higher levels of testosterone. These observations have been reported by other workers investigating the fertility- enhancement potential of withania and other herbs and minerals.[65]

Antibacterial and antifungal activity: Results of a 2011 Indian study reveal that extracts of withania show great antimicrobial potential against test microorganisms. Candida albicans was found to be the most susceptible organism followed by Staphylococcus aureus, Proteus mirabilis, Escherichia coli and Pseudomonas aeruginosa.[66]

A study on the antibacterial activity of withania has found that oral administration of the aqueous extract of withania successfully obliterated salmonella infection in mice as revealed by increased survival rate, as well as less bacterial load in various vital organs of the treated animals. Both aqueous as well as alcoholic extracts of the plant (root as well as leaves) were found to possess strong antibacterial activity against a range of bacteria in vitro. The methanolic extract was further subfractionated using various solvents and the butanolic sub-fraction was found to possess maximum inhibitory activity against a spectrum of bacteria including Salmonella typhimurium. In contrast to the synthetic antibiotic (chloramphenicol), these extracts did not induce lysis (breaking down of the cell wall) on incubation with human erythrocytes, advocating their safety to the living cells. Finally, the antibacterial efficacy of the extracts isolated from plant (both root and leaves) was determined against experimental salmonellosis in mice.[67]

The methanol and hexane extracts of both leaves and roots of withania were found to have potent antibacterial activity when evaluated in vitro for the antibacterial/ synergistic activity against Salmonella typhimurium and Escherichia coli.[68]

Cardiovascular activity: The antioxidant and anti-apoptotic (preventing cell death) properties of withania may contribute to its cardioprotective effects. An animal study was undertaken to evaluate the cardioprotective mechanisms of withania, in the setting of ischemia (decreased blood flow and oxygen to the heart muscle) and reperfusion injury (the tissue damage caused when blood supply returns to the tissue after a period of ischemia). Rats receiving prior treatment with withania favourably restored the myocardial oxidant-antioxidant balance, exerted marked anti-apoptotic effects and reduced myocardial damage.[69]

Hypoglycaemic activity: Withania is a potential source of hypoglycaemic, diuretic and hypocholesterolaemic agents following a human study. Six mild noninsulin-dependent diabetes mellitus (NIDDM) subjects and six mild hypercholesterolaemic subjects were treated with powdered withania root for 30 days. Suitable parameters were studied in the blood and urine samples of the subjects along with dietary pattern before, and at the end of, the treatment period. Decrease in blood glucose was comparable to that of an oral hypoglycaemic drug. Significant increases in urine sodium, urine volume, and significant decreases in serum cholesterol, triglycerides, LDL (low density lipoproteins) and VLDL (very low density lipoproteins) cholesterol were observed. Clinical observations revealed no adverse effects.[70]

An animal study suggests that the aqueous extract of withania normalises hyperglycaemia in NIDDM (non- insulin-dependent diabetes mellitus) rats by improving insulin sensitivity. Treatment with withania reduced the elevated levels of blood glucose, glycosylated haemoglobin and insulin in the NIDDM rats. Withania treatment markedly improved the insulin sensitivity index that was significantly decreased in NIDDM control rats. There was a noticeable rise in the homeostasis model assessment of insulin resistance (HOMA-R) in NIDDM control rats whereas withania treatment considerably prevented the rise in HOMA-R in NIDDM-treated rats.[71]

The activity of an ethanolic extract of withania is comparable to metformin, a known antiglycating agent, a recent study has found. Therefore, withania could have a therapeutic role in the prevention of

glycation induced pathogenesis in diabetes mellitus and ageing. Modification of collagen such as non-enzymatic glycation and cross-linking plays an important role in diabetic complications and age-related diseases. The study evaluated the effect of withania on glucose-mediated collagen glycation and cross-linking in vitro.[72]

Hypolipidaemic activity: Hypocholesteraemic and antioxidant effects of withania were investigated in hypercholesteraemic rats. When the root powder of withania was added to the diet at 0.75 and 1.5 gm/rat/day, hypercholesteraemic animals registered significant decreases in total lipids, cholesterol and triglycerides in plasma. On the other hand, significant increases in plasma HDL-cholesterol levels, HMG- Coenzyme A reductase activity and bile acid content of liver were noted in these animals. A similar trend was also noted in bile acid, cholesterol and neutral sterol excretion in the hypercholesteraemic animals with withania administration. Further, a significant decrease in lipid-peroxidation occurred in withania administered hypercholesteraemic animals when compared to their normal counterparts. It appeared that withania is also effective in normal subjects for decreasing lipid profiles.[73]

Drug withdrawl: A 2014 study has demonstrated the therapeutic potential of withania as a valuable adjuvant agent in opioid dose- sparing therapies. Previous studies have demonstrated that withania prevents the development of tolerance to the analgesic effect of morphine (see below).[74]

The 2014 study investigated whether withania extract (100mg/kg, intraperitoneal injection) may also modulate the analgesic effect induced by acute morphine administration (2.5, 5, 10mg/kg, beneath the skin) in the tail-flick and in the hot plate tests, and if it may prevent the development of 2.5mg/kg morphine-induced rebound hyperalgesia (increased sensitivity to pain) in the low intensity tail-flick test. To characterise the receptor(s) involved in these effects, the authors studied, by receptor-binding assay, the affinity of withania for opioid, cannabinoid, glutamatergic (NMDA), GABAergic (GABAA, GABAB), serotoninergic and adrenergic receptors. The results demonstrated that withania alone failed to alter basal nociceptive (pain) threshold in both tests, withania pre-treatment significantly protracted the antinociceptive effect induced by 5 and 10mg/kg of morphine only in the tail-flick test, withania pre- treatment prevented morphine-induced hyperalgesia in the low intensity tail-flick test, and withania exhibited a high affinity for the GABAA and moderate affinity for GABAB, NMDA and opioid receptors. Withania prolongs morphine-induced analgesia and suppresses the development of morphine-induced rebound hyperalgesia probably through involvement of GABAA, GABAB, NMDA and opioid receptors.[75]

A previous study investigated whether morphine withdrawal-induced spine reduction in the nucleus accumbens (a region in the brain) is affected by the administration of a withania extract. Rats were chronically treated with withania along with morphine or saline and, upon spontaneous (1 and 3 days) or pharmacologically precipitated withdrawal, their brains were fixed in Golgi- Cox stain for confocal microscopic examination. In a separate group of animals, withania was administered during three days of spontaneous withdrawal. Withania treatment reduced the severity of the withdrawal syndrome when given during chronic morphine but not during withdrawal. In addition, treatment with withania during chronic morphine, but not during withdrawal, fully prevented the reduction of spine density in the nucleus accumbens shell in spontaneous and pharmacologically precipitated morphine withdrawal. These results indicate that pre-treatment with withania protects from the structural changes induced by morphine withdrawal potentially providing beneficial effects on the consequences related to this condition. Therefore, treatment with withania in the weeks leading up to a planned opiate withdrawal may be beneficial.[76]

Thryoid activity: A 32-year-old healthy woman developed thyrotoxicosis (the hypermetabolic clinical syndrome which occurs when there are elevated serum levels of T3 and/or T4) while taking capsules that contained withania for symptoms of chronic fatigue. She was not taking any other remedies or medications. During the first few weeks she took the capsules only occasionally without any symptoms but, after increasing the dose, she experienced clinical symptoms indicative of thyrotoxicosis. This was confirmed by laboratory assessment. The symptoms resolved spontaneously after discontinuation of the withania capsules and laboratory values normalised. To the authors knowledge this relationship has not been reported previously in humans. Data from animal studies has suggested that withania can increase serum concentrations of thyroid hormones. This case study suggests that thyrotoxicosis is a potentially serious side effect of withania.[78]

Indications: Anxiety, insomnia, stress especially with debility and nervous exhaustion, convalescence, weakness, wasting disorders, especially in children and the elderly, exhaustion associated with reduced iron levels. Conditions associated with aging such as memory loss, dementia, Alzheimer's disease, Parkinson's disease. Chronic diseases, especially of an inflammatory nature, such as arthritis, asthma and psoriasis. Anaemia, Impotence due to stress and poor vitality, Possible prophylactic in cancer and adjunctive treatment during chemotherapy, Assistance in the withdrawal of addictive drugs.

Toxicity: Withania is generally safe when taken in the prescribed dosage range and toxicity studies reveal that it appears to be a safe compound. Large doses have been shown to cause gastrointestinal upset, diarrhoea and vomiting.[80]

Use in Pregnancy: Large doses of withania may possess abortifacient properties therefore it should not be taken during pregnancy.[81]

Contraindications: People who are sensitive to the Solanaceae family should use this herb with caution.[82]

Drug Interactions: There are reports that withania may potentiate the effects of barbiturates (central nervous system depressants) and benzodiazepines (a group of drugs called minor tranquillisers prescribed by a doctor to help people with anxiety or sleep problems e.g. diazepam – Valium; oxazepam – Serepax; nitrazepam – Mogadon; temazepam; flunitrazepam – Rohypnol) therefore caution should be used if taking this combination.[83,84]

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